Review Article

Analysis of Interventional Clinical Research Protocols Related to Coronavirus Disease 2019 and Future Expectations

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Abstract

Coronavirus disease 2019 (COVID-19) is a newly emerging infectious disease. After its outbreak, researchers started a large number of clinical interventional studies, using a variety of interventions to study the different types of COVID-19 cases. In this article, we searched the websites of Chinese Clinical Trial Registry, ClinicalTrials.gov, etc., to study the publicly registered research information. Through the classification and summary of interventional methods, evaluation indicators, research design, etc., this article provided readers with the outline of clinical research about COVID-19, and looked forward to the scientificity, feasibility, and future evidence of the clinical researches.

Keywords: Clinical trial protocol, coronavirus disease 2019, interventional study

Introduction

Since December 2019, Coronavirus Disease 2019 (COVID-19) has erupted in many places around the world, which is strong infectious and highly epidemic. Subsequently, the National Health Commission included pneumonia infected by the novel coronavirus into the Class B infectious diseases stipulated in the *Law of the People's Republic of China on Prevention and Control of Infectious Diseases*, and managed them as a Class A infectious disease.[1] On February 21, 2020, pneumonia infected with a new type of coronavirus was uniformly named as coronavirus disease 2019 (COVID-19).[2] By February 23, 2020, the number of confirmed COVID-19 cases in China reached 77,056. The number of deaths reached 2446. During the epidemic emergency response, the Chinese government launched a series of studies, including rapid and collaborative researches on viral gene sequence sequencing, pathogen detection, disease epidemic monitoring and early warning, rapid screening, clinical diagnosis and treatment, convenient disinfection, new drugs (vaccine) R and D and rapid preparation, traditional Chinese medicine (TCM) application, personal protection standard formulation and protection product development, emergency health science and psychological intervention, big data, and public health decision support, providing strong, timely, and effective technical support and medical guarantees for the decision-making of the prevention and control of the epidemic.

At the same time, in the initial period of the epidemic and the emergency response period, during just over 2 months, researchers around the world carried out a lot of researches around the epidemic and published nearly 300 papers, mainly epidemiological research and etiology. There were nearly fifty guideline literatures and thirty TCM literatures. The number of research articles on disease diagnosis and treatment was very small, with <10 articles. Due to the lack of clinical evidence, although the central government and local governments have issued multiple versions of the diagnosis and treatment plan, the current clinical treatment practice is still based on empirical treatment.

In order to describe the future clinical evidence of COVID-19, this article analyzed the COVID-related treatment studies that

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Access this article online

Quick Response Code:

Website: www.wjtcm.net

DOI: 10.4103/wjtcm.wjtcm_11_20

Received: 24-02-2020, **Accepted:** 26-02-2020 **Published:** 12-03-2020

How to cite this article: Wang YF, Du M, Su R. Analysis of interventional clinical research protocols related to coronavirus disease 2019 and future expectations. World J Tradit Chin Med 2020;6:139–44.

have been registered on the public website, evaluated its project design and feasibility, and analyzed its future results.

As of February 22, 2020, a total of 265 clinical studies were published in the Chinese Clinical Trials Registry and ClinicalTrials.gov [Table 1].

The current research around COVID-19 was mainly focused on epidemiological research, diagnostic research, and interventional clinical research. Considering the importance of interventional clinical research in the current epidemic situation, this article mainly studied and analyzed it. The main analysis content included compulsory items of registration and key provisions of research protocol, such as research objectives and evaluation indicators, interventional methods, sample size, and research design.[3]

Basic Situation of Interventional Clinical Research

This article summarized the status of interventional clinical research registered on Chinese Clinical Trial Registry and other websites before February 22, 2020. The classification and summary results are shown in Table 2.

In interventional clinical research, interventional methods were mainly focused on drug interventions and medical operation interventions, among which drug interventions were mainly chemical drugs, Chinese medicinal herbs, and biological products. Chinese medicinal herbs were mainly divided into medication based on syndrome differentiation and Chinese patent medicine. Medical operation interventions mainly included extracorporeal membrane oxygenation (ECMO) technology, ultrashort wave, and Daoyin. Most of the registered studies have passed ethical review and are eligible to start clinical research.

By summarizing the research subjects, as shown in Table 3, it was found that the research subjects were mainly adults, and there were only ten child-related researches. Because some studies involved multiple subtypes, such as mild, common, or severe, the number of whole studies exceeds the total number of studies. In terms of the severity of the disease, the research subjects were mainly concentrated in mild or common

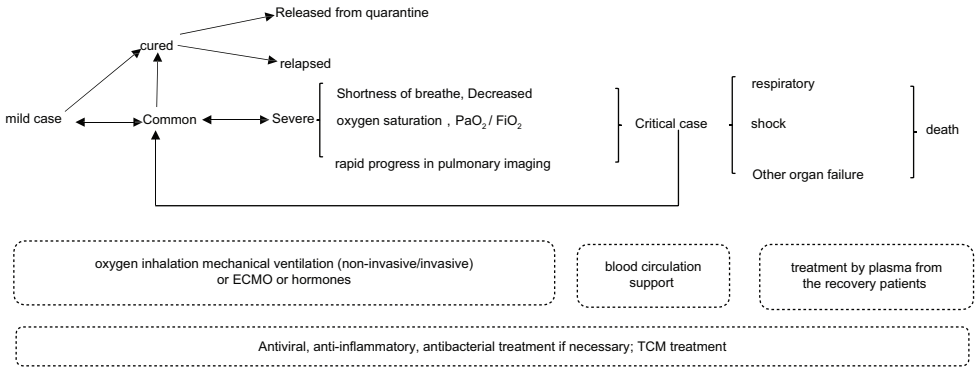

Figure 1: Coronavirus disease 2019 development

Table 1: Research status registered in Chinese Clinical Trial Registry and other websites (till February 22, 2020)

	Research classification	Number of registrations	Number of TCM-related researches	Number of child-related researches
Chinese Clinical Trial Registry (www.chictr.org.cn)	Epidemiological research	13	1	2
	Interventional clinical research	162	67	7
	Diagnostic clinical research	20	1	2
	Psychological clinical research	10	1	-
	Preventive clinical research	11	10	3
	Other clinical research	1	-	-
ClinicalTrials.gov (clinicaltrials.gov)	Epidemiological research	2	-	1
	Interventional clinical research	35	5	5
	Diagnostic clinical research	8	-	7
	Psychological clinical research	1	-	1
	Preventive clinical research	-	-	-
	Other clinical research	1	-	
CDE (www.chinadrugtrials.org.cn)		0	-	-
Total		274	85	28

1: In this data compilation, a total of 265 research protocols were included, of which the total number exceeded 265 due to the overlap of some research classifications. Among them, interventional research overlaps with other classifications, 2: Other interventional research cannot retrieve specific information from the website. NMPA CDE: National Medical Products Administration, Center for drug evaluation, TCM: Traditional Chinese medicine

Table 2: Status of interventional clinical research (till February 22, 2020)

	Classification of intervention	Number of registered research	Number of child-related research	Number of passing ethical review
Chinese Clinical Trial Registry	Chemical drugs	65	-	59
	Biological product	39	-	29
	Chinese medicinal herbs	64	5	58
	Medical operation	13	-	2
	Others	3	-	3
ClinicalTrials.gov	Chemical drugs	19	2	19
	Biological product	12	1	12
	Chinese medicinal herbs	4	1	4
	Medical operation	-	-	-
	Others	1	1	1

1: The vast majority of studies were based on standard treatments, plus relevant interventions. The standard treatments were performed according to national COVID-related diagnosis and treatment guidelines, 2: Research ethics. COVID: Coronavirus disease

Table 3: Research object (till February 22, 2020)

Number	Research subjects	*n*	Notes
1	Mild/common case related	143	Some studies related to suspected/severe cases
2	Severe case related	42	
3	Suspected case related	12	
4	Others	15	

COVID-19 patients, accounting for 72.5%, and severe cases accounting for 21.3%. In addition, some of the study patients were suspected cases or healthy people.

Efficacy Evaluation Indicators

The objective of clinical research is mainly achieved through evaluation indicators. The evaluation indicator determines the degree of influence of the research results on clinical decision-making, and Whether the evaluation index is suitable or not will directly affects the value of the research conclusion.[4] The primary outcome measures were those clinical events that had the greatest impact on the patient, and that the patient was most concerned about or wanted to avoid, such as death, acute myocardial infarction, stroke, exacerbation of heart failure, damage to vital organs, and recurrence of the disease. The secondary outcome indicators are indicators that can reflect the changes in the primary outcome indicators caused by the intervention and can be substituted for the primary outcome indicators under certain conditions.[5]

As COVID-19 is a new outbreak of infectious disease, the epidemic situation has not been resolved so far. In this case, the observation of the evaluation indicators also reflects the concerns of clinical experts in clinical decision-making, the judgment of prognosis, and the cognition of clinical issues of Chinese medicinal herbs. This article classified and summarized the clinical treatment efficacy evaluation indicators and sorted them [Tables 4 and 5]. Generally speaking, the evaluation indicator is focused on the disease index in the current research, which is consistent with the reports in literature,[6] and the relevant indicators have a high degree of objectivity.[7]

The current classification and summary results of the evaluation indicators were similar to the *COVID-19 Diagnosis and Treatment Scheme (Trial Version 6)*,[8] which lays a good foundation for COVID-19-related research. According to the *COVID-19 Diagnosis and Treatment Scheme (Trial Version 6)*, the clinical classification of COVID-19 includes mild, common, severe, and critical. Most patients have a good prognosis, and a few patients are critically ill. The disease development is as follows shown in [Figure 1].

According to this diagnosis and treatment plan, in mild and common patients, the main diagnosis and treatment outcome is recovery or deterioration of the disease to severe. The standard for recovery from illness is based on the provisions of the *Quarantine Release and Discharge Standards*. From the current knowledge of the disease, even if it meets the relevant standards, it should still be quarantined for 14 days after the disease recovers before it can be released. Due to the timing of the outbreak virus detection and sample collection, false-negative results may occur,[9] so the use of virological testing as the main evaluation index has certain limitations, and its negative conversion cannot fully explain the recovery of the disease.

For severe patients, the outcome is mainly recovery from disease, transition to common case, or transition to critical case. The treatment methods can be further detailed to whether to accept noninvasive mechanical ventilation, whether to accept invasive mechanical ventilation, and whether to accept hormonal therapy. For critical cases, the primary outcome is survival or mortality. According to the treatment method, it can be further refined into whether to receive ECMO treatment or blood circulation support.

Regardless of whether it is mild or severe, the evaluation point of the study endpoint was 14–30 days, and some studies observed the data on the 90th day. It would be better to follow-up once after recovery to assess whether it has relapsed.

Research Interventions and Sample Sizes

Table 6 summarizes the main drugs and related sample

Table 4: Evaluation indicators of mild/common case-related studies (till February 22, 2020)

Number	Evaluation indicators	Ordering of primary evaluation indicators	Ordering as evaluation indicators
1	Virological testing (negative/decreased viral load, etc.)	1	1
2	Time or proportion of disease cured (recovery)	2	4
3	Improved clinical symptoms	3	2
4	Outcome of the disease (severe case, ICU, critical cases, and death)	4	3
5	Body temperature returns to normal	5	5
6	Oxygen index/oxygen absorption/oxygen partial pressure, etc.	6	6
7	Improved chest radiography[7]	7	7
8	Pneumonia Severity Index	8	10
9	Length of hospitalization	9	8
10	Adverse events	10	9

ICU: Intensive care unit

Table 5: Efficacy evaluation indicators of severe/critical case-related studies (till February 22, 2020)

Number	Evaluation indicators	Ordering of primary evaluation indicators	Ordering as evaluation indicators
1	Clinical improvement	1	2
2	Outcomes of the disease (critical case, mechanical ventilation, ECMO, and death)	2	1
3	Lung Injury Score	3	7
4	Pulmonary imaging evaluation	4	5
5	Blood gas analysis	5	3
6	Body temperature	6	6
7	Virological testing (negative/decreased viral load, etc.)	7	4
8	Blood routine	8	8

ECMO: Extracorporeal membrane oxygenation

sizes used in the research intervention. The selection of related drugs was close to the reports in literature,[10] while Chinese medicinal herbs and some new drugs are innovative. Chemical drug research involved 32 types, and their concentration was relatively good, mainly concentrated on drugs such as lopinavir/ritonavir, interferon, chloroquine, hydroxychloroquine, glucocorticoids, and Remdesivir. Among them, glucocorticoids are mainly used in severe or critically ill patients. The concentration of biological products was relatively poor, and some drugs with relatively high concentration were listed in this table. Chinese medicinal herbs were mainly Chinese patent medicine and medication based on syndrome differentiation treatment, such as Lianhua Qingwen granules.[11] Other interventions listed ECMO technology and early tracheal intubation mainly used in critically ill patients and rehabilitation technology and Daoyin mainly used in patients during rehabilitation.

Research Design

As of the time of the article's summary, most studies used randomized controlled clinical study designs, as shown in Table 7. There were 139 randomized controlled studies, accounting for 70.6%. In this part of the study, 33 were multicentric clinical studies, 94 were 1–2 research centers, and 12 were undisclosed.

Of the total of 58 items of the other two types of clinical research, 13 items were multicentric clinical studies, 29 were 1–2 research centers, and 15 were undisclosed research center information.

Analysis of the Value of Clinical Research Related to Corona Virus Disease 2019

In view of the above, most clinical studies have selected key evaluation indicators and appropriate treatment cycles. Intervention drug selection is diverse, providing a good basis for drug screening for COVID-19. However, due to the sudden outbreak and lack of awareness of the disease and quarantine measures, COVID-19-related clinical research was conducted in the absence of a top-level design, and the research foundation and research team were not mature enough. However, this is inevitable in the current environment.

From the perspective of program design, the scientificity evaluation of related research[12] is mainly based on the following factors: whether basic treatment (or standard treatment or conventional treatment) can avoid bias; whether the results of virological testing can reduce the probability of false negatives; whether there is bias after random stratification of critically ill patients; whether the researcher's bias control is good; whether the specific definition of curative effect evaluation indicators is uniform and objective; whether the sample size is sufficient, etc.

Table 6: Research interventions (till February 22, 2020)

Intervention type	Number	Intervention methods	Number of researches involved	Sample size
Chemical drugs	1	Lopinavir/ritonavir	19	2074
	2	Interferon	11	1301
	3	Chloroquine	10	496
	4	Hydroxychloroquine	8	750
	5	Glucocorticoids	6	640
	6	Ribecvir	3	572
Biological products	1	Mesenchymal stem cell	5	185
	2	ASC09	4	200
	3	Drugs that regulate intestinal flora	4	240
	4	Novaferon	2	320
	5	Anti-SARS-CoV-2 virus-inactivated plasma	3	90
Chinese medicinal herbs	1	Treatment based on TCM syndrome differentiation	29	3682
	2	Shuanghuanglian oral solution	2	320
	3	Xiyanping	2	293
	4	Lianhua Qingwen capsules	1	300
	5	Kangbingdu particles/oral solution	2	172
	6	Ganke Shuangqing capsules	1	240
	7	Shenfu injection	1	150
	8	Xuebijing	1	200
	9	Xiaoer Huatan Zhike granules	1	100
	10	Shenqi Fuzheng injection	1	80
Others	1	Extracorporeal membrane oxygenation technology	2	140
	2	Rehabilitation technology	2	200
	3	Early tracheal intubation	1	200

1: The above drugs were listed in both the control group and the experimental group, 2: Most of the studies were based on the standard treatment and plus the above drugs. Due to the unclear specifics of standard treatments, we cannot evaluate the adequacy of their combination. TCM: Traditional Chinese medicine

Table 7: Research design information (till February 22, 2020)

Number	Intervention	Number of researches involved	Notes
1	Observational research	34	
2	Nonrandomized controlled study	24	
3	Randomized controlled study	139	There were 14 double-blind designs and 6 single-blind designs
	Total	197	

From the perspective of the study design and sample size,[13] the single sample size of most studies is relatively small. Due to the lack of basic data, the calculation of related sample sizes is also difficult. Therefore, for most studies that have been registered, the research data is likely to be inadequate and can only be evaluated as an exploratory study. Of course, this is also the work that must be done before conducting large-scale research.

From the perspective of the research organization, the feasibility of the related research[14] is mainly evaluated based on the following factors: whether the urgently mobilized research is compatible with clinical practice; whether sufficient cases can be included in a short period of time or with a reduction in newly diagnosed patients (especially in centers that have not passed the ethical review); whether the ethics committee is active in the attention and cooperation for the research; whether the research team can guarantee the compliance of the plan in the event of an epidemic situation; whether the research quality can be guaranteed in the case of heavy diagnostic tasks, etc.

From the current clinical research plan, there are three types of clinical evidence in future, which are worthy of attention.[15]

The first type is a randomized controlled blinded study with a sufficient sample size and appropriate evaluation indicators, such as for the research on Remdesivir, lopinavir/ritonavir group, abidol, chloroquine, and hydroxychloroquine. These studies can provide definitive evidence for the effectiveness of the test drugs, and can also be mutually corroborated by relatively independent research data or meta-analysis of these studies to obtain high-level research evidence.

The second type is research without blind design, but with sufficient sample size and appropriate evaluation indicators, such as Chinese medicinal herbs based on syndrome differentiation, Lianhua Qingwen capsules, glucocorticoids, ECMO technology, and interferon. In future, data consolidation analysis and cross-validation of these studies can be used to provide real-world research evidence for the development of COVID guidelines.

The third type is a small sample study using a randomized controlled design, which can be used as an exploratory study to provide a basis for further screening of interventional methods.

Conclusions

Overall, <50 days after the outbreak, researchers, with government and business funding, quickly launched nearly 197 interventional clinical studies and 68 clinical studies related to TCM, which is the first time in the history of Chinese medical care. Related researches are very efficiently organized. It is hoped in future that, through data sharing and data mining, researchers can further improve the quality of research evidence and come up with better clinical evidence for COVID-19.

Acknowledgments

This work is supported by the National Major Scientific Research Project (2017ZX10305501).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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